GEORGIA INSTITUTE OF TECHNOLOGY — OFFICE OF CONTRACT ADMINISTRATION

PROJECT ADMINISTRATION DATA SHEET

[X] ORIGINAL [ ] REVISION NO. _____

Project No. E-16-679 (R5823-0A0) GTRI/GIT DATE 9 /10 / 84

Project Director: Dr. Don P. Giddens School/~~Lab~~ AE

Sponsor: National Science Foundation

Type Agreement: Grant No. MEA-8312391

Award Period: From 6/1/84 To 11/30/84 (Performance) 2/28/85 (Reports)

Sponsor Amount:	This Change	Total to Date
Estimated:	$ 19,984	$ 19,984
Funded:	$ 19,984	$ 19,984

Cost Sharing Amount: $ 200 Cost Sharing No: E-16-361 (F5823-0A0)

Title: "Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis"

ADMINISTRATIVE DATA OCA Contact Lynn Boyd X4820

1) Sponsor Technical Contact:

George K. Lea
Fluid Mechanics Program
Mechanical Engineering and Applied Mechanics
National Science Foundation
1800 G Street
Washington, D.C. 20550
(202)357-9542

2) Sponsor Admin/Contractual Matters:

W. Jeffrey Crenshaw
Grants Official
National Science Foundation
1800 G. Street
Washington, D.C. 20550
(202)357-9626

Defense Priority Rating: n/a Military Security Classification: n/a

(or) Company/Industrial Proprietary: n/a

RESTRICTIONS

See Attached NSF Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval – Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT

COMMENTS:

*Includes 2 month unfunded flexibility period.
This is a continuing grant (has been approved for approximately 40 months). This 7 month grant provides initial funding of 3 year continuation.

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FORM OCA 4:383

GEORGIA INSTITUTE OF TECHNOLOGY OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION/CLOSEOUT SHEET

Date July 23, 1986

Project No. E-16-679 (R5823-0A0) School/~~Lab~~ AE

Includes Subproject No.(s) N/A

Project Director(s) D. P. Giddens GTRC / ~~GIT~~

Sponsor National Science Foundation

Title Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis

Effective Completion Date: 6/30/86 (Performance) 6/30/86 (Reports)

Grant/Contract Closeout Actions Remaining:

- [X] None
- [ ] Final Invoice or Final Fiscal Report
- [ ] Closing Documents
- [ ] Final Report of Inventions
- [ ] Govt. Property Inventory & Related Certificate
- [ ] Classified Material Certificate
- [ ] Other

This account is being terminated due to the PI transferring to the School of Mechanical Engineering. Project effort is continuing under Account E-25-687.

Continues Project No. N/A Continued by Project No. E-25-687 (R5823-0A1)

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FORM OCA 69.285

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Grant No. MEA-8312391

PROGRESS REPORT: JUNE - SEPTEMBER, 1984

During this period four graduate research assistants were employed to work on this project. The following were accomplished:

1. A series of laser Doppler velocimeter (LDV) studies in steady and pulsatile flow through a plexiglas tube with a 90% axisymmetric constriction was performed. The data are being analyzed with respect to their relationship to monkey coarctation studies and to the distribution of wall shear stress in the models.

2. Work on developing the capability to construct flow models using compliant material was initiated. We are studying the use of silicone rubber materials which are transparent so that the LDV can be employed for velocity measurements. The initial casts were of straight flexible tubes and appear to have sufficiently good optical qualities that will allow use of the LDV.

3. Work continued on development of a library of FORTRAN computer programs which contain autoregressive signal analysis and phase-shift averaging routines. We are also redesigning our data acquisition equipment and software to speed up the data transfer to the CYBER system.

4. A manuscript entitled "Pulsatile flow and atherosclerosis in the human carotid bifurcation: Positive correlation between plaque localization and low and oscillatory shear stress" by D. N. Ku, D. P. Giddens, C. K. Zarins and S. Glagov has been revised for the journal Arteriosclerosis. The reviewers have recommended that this manuscript be published when the revisions are completed.

Don P. Giddens, Ph.D.
Principal Investigator

DPG/ed

5/12/84

Summary of Progress

The overall goals of the research are to advance basic knowledge in unsteady fluid dynamics and to identify specific fluid mechanical mechanisms which contribute as causative factors to the initiation and progression of atherosclerosis. The Georgia Tech program is a companion study to a project underway in the Departments of Surgery and Pathology at the University of Chicago Medical School under the direction of Drs. C. K. Zarins and S. Glagov. Fluid dynamic modeling is carried out at Georgia Tech while appropriate biological studies are performed at the University of Chicago. Investigators meet at least bi-monthly to work together on the program. Investigations completed since the last progress report have yielded several definitive and important results. We previously reported that, based upon our initial studies, two factors previously thought by many to be atherogenic - high wall shear stress and turbulence - were actually unrelated to the initiation of atherosclerosis. Also, we tentatively identified low wall shear and oscillating wall shear as being strongly associated with early plaque localization. Since then we have completed a series of correlations between fluid dynamic measurements in models and morphometric descriptions of plaque location. These studies have led us to conclude definitively that atherogenesis is not related to turbulent flow or high wall shear stress but rather, moderately high values of wall shear stresses which do not change direction during the cardiac cycle appear to offer protection from the development of plaques. A remarkable finding which arose from these studies is the fact that the artery tends to adapt its size to maintain these moderate wall shear stress values. Thus, the implication is that the structure of the arterial wall can be modified by changes in the local fluid dynamic environment. This has important ramifications in understanding not only the genesis of atherosclerotic plaques but also their progression. We have concluded that either low wall shear or oscillating wall shear creates a favorable microenvironment for atherosclerosis, possibly through either long residence time of circulating lipoproteins near endothelial surfaces or through an mechanical interaction of plasma protein molecules with lipoproteins in the fluid layer adjacent to the artery wall. Current research is directed toward exploring these two possibilities. The basic fluid dynamic studies in pulsatile flow fields have led to an apparently new method of quantitatively describing flow disturbances in the frequency domain using autoregressive methods of spectral estimation. These have been demonstrated to be more reliable and to have less variance when dealing with transient disturbances than the traditional Fourier methods. The studies have also shown that decomposing velocity into ensemble average and random components is flawed when pulsatile flows are being examined, particularly at the Reynolds numbers characteristic of physiological blood flow. This finding has important implications in that the determination of Reynolds stresser associated with turbulent fluctuations cannot by decoupled from laminar, unsteady fluctuations.

E-16-679

ABSTRACT: "Hemodynamics and Atherogenesis at the Human Carotid Bifurcation," D. N. Ku

Atherosclerosis is a widespread disease accounting for almost half of the deaths in the western world. This complicated disease affects only specific arteries and is highly localized within these vessels. The selective localization of atheromatous plaques strongly suggests that hemodynamics is an initiating factor. The human carotid artery bifurcation has an unusual internal carotid sinus enlargement and is the site of stroke-producing atherosclerosis. A large scale model of the carotid bifurcation was constructed based on average dimensions permitting detailed studies of the hemodynamic environment. Unsteady, pulsatile flow with physiologic partitioning between the branches is incorporated.

Visualization using hydrogen bubbles reveals the evolving nature of secondary flow in the carotid sinus. The size of a separated reverse flow region contracts and enlarges with each cycle. Paired helices develop in the sinus and move in the retrograde direction in late systole. Flow in the distal internal carotid is dispersive indicating breakup of the large helices.

Flow field measurements using a laser Doppler anemometer quantitatively describe the dominant, unsteady behavior during systole. Velocity and shear stress at the inner wall are high and unidirectional throughout the cycle. At the outer wall, the flow is forward in early systole but reverses in later systole. The magnitude of maximum and minimum shear stress at the outer wall reaches the same level seen in the common carotid during diastole. The side wall

predominantly axial to a predominantly circumferential direction. These helices create steep velocity gradients which lead to coherent structures of a discrete frequency at the distal sinus.

Early intimal thickening from atherosclerosis in human carotid specimens is quantitatively mapped and locates early plaque at the outer and side wall of the sinus. Although several hemodynamic variables correlate favorably with intimal thickness, oscillatory shear stress proves to yield the strongest relationship ($r=0.92$, $p<.001$). Increased residence time of particles may also augment the development of plaque at the outer wall. A new, comprehensive hypothesis for atherogenesis is proposed based on oscillatory shear stresses and increased particle residence times.

ABSTRACT: "Ordered and Random Structures in Pulsatile Flow Through Constricted Tubes," B. Lieber.

The poststenotic flowfield in a rigid tube was investigated under pulsatile conditions. The motivation for this study originates in hemodynamics where flow behavior is linked to evolution of cardiovascular diseases and is considered a possible tool for early detection of arterial diseases such as atherosclerosis.

The pulsatile waveform employed in the recent experiments was sinusoidal, and three contoured constrictions with 50 percent, 75 percent and 90 percent area reduction were investigated. The fluid dynamic similarity parameters were chosen to represent conditions found in large arteries of humans and experimental animals, using a Reynolds number range of 200 to 1000 and a frequency parameter value of 5.3.

The present investigation employs the analysis techniques of autoregressive modeling, correlation methods and phase-shift averaging in order to extract the maximum information about flow behavior. Analysis focuses on identification and representation of coherent flow disturbances, and examination of the influence of core flow behavior on the cyclic wall shear stress.

Results of this study show an intimate relation between wall shear behavior and that of the core flow for all three cases of stenosis. Flow disturbances in the core flow for 50 percent and 75 percent constriction are mild and occur at low magnitudes and in a frequency range characteristic of the onset of transition. Core flow phenomena for the cases of 50 percent and 75 percent are well reflected in the behavior of the wall shear stress. Velocity

fluctuations in the poststenotic flowfield for the case of 90 percent stenosis are intense, exhibiting several interesting features including a starting structure, puff formation and vortex shedding at different excitation frequencies of the shear layer. The wall shear behavior for the 90 percent stenosis clearly reflects core flow phenomena.

Phase-shift averaging, a useful technique for extraction of coherent flow disturbances, was found incapable of separating random variations from the velocity data for the purpose of analysis of random velocity fluctuations. "Trend-removing" on the other hand, a method adopted for this study, was shown to be appropriate for analysis of flowfields such as encountered in the present study.

Autoregressive modeling was demonstrated to be superior to the fast Fourier transform technique for spectrum estimation when applied to pulsatile flow. Autoregressive spectra sharply display the main features of the flow and exhibit a low variance in the spectral estimates. The use of autoregressive modeling eliminates the ambiguities presented in a fast Fourier transform spectrum and reduces the number of ensemble averaged cycles needed to obtain a reliable spectrum.

B. PUBLICATIONS

The following have been published since the termination of our previous NSF Grant MEA-7921551. We continued the research at our own expense until the award of the grant MEA-83-12391.

1. C. K. Zarins, D. P. Giddens, B. K. Bharadvaj, V. S. Sottiurai, R. F. Mabon and S. Glagov; "Carotid Bifurcation Atherosclerosis: Quantitative Correlation of Plaque Localization with Flow Velocity Profiles and Wall Shear Stress," Circulation Research, Vol. 53, No. 4, 1983, pp. 502-514.

2. S. A. Ahmed and D. P. Giddens; "Flow Disturbance Measurements Through a Constricted Tube at Moderate Reynolds Numbers," Journal of Biomechanics, vol. 16, 1983, pp. 955-963.

3. S. Glagov, C. K. Zarins, K. E. Taylor, R. A. Bomberger and D. P. Giddens; "Evidence that High Flow Velocity and Endothelial Disruption are not the Principal Factors in Experimental Plaque Localization," Fluid Dynamics as a Localizing Factor in Atherosclerosis, Springer-Verlag, Berlin, 1983.

4. D. P. Giddens, C. K. Zarins, S. Glagov, B. K. Bharadvaj and D. N. Ku; "Flow and Atherogenesis in the Human Carotid Bifurcation," Fluid Dynamics as a Localizing Factor in Atherosclerosis, Springer-Verlag, Berlin, 1983.

5. S. A. Ahmed and D. P. Giddens; "Pulsatile Poststenotic Flow Studies with Laser Doppler Anemometry," Journal of Biomechanics, Vol 17, No. 9, 1984, pp. 695-705.

6. M. Casty and D. P. Giddens; "25 + 1 Channel Pulsed Ultrasound Doppler Velocity Meter for Quantitative Flow Measurements and Turbulence Analysis," Ultrasound in Medicine and Biology, Vol. 10, 1984, pp. 161-172.

7. D. P. Giddens and R. I. Kitney; "Blood Flow Disturbances and Spectral Analysis," Noninvasive Diagnostic Techniques in Cardiovascular Disease, 3rd Edition, ed. by G. F. Bernstein, C. V. Mosby Co., St. Louis, 1985, pp. 55-68.

8. D. N. Ku, D. P. Giddens, C. K. Zarins and S. Glagov; "Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation: Positive Correlation between Plaque Localization and Low and Oscillating Shear Stress," Arteriosclerosis, Vol. 5, 1985, pp. 293-302.

9. C. K. Zarins, M. A. Zatina, D. P. Giddens, D. N. Ku, S. Glagov; "Shear Stress Regulation of Artery Lumen Diameter in Experimental Atherogenesis," Journal of Vascular Surgery (Accepted).

I. Don P. Giddens

A. Current Support

1. Source: Johnson and Johnson Corporation

Title: Pediatric Hemodynamics and Cardiovascular Control

Amount: $178,000

Period: 11/1/82 - 10/31/86

Effort: 10% Academic
10% Summer

Location: Georgia Institute of Technology, School of Mechanical Engineering

Emory University, Egleston Hospital and Grady Memorial Hospital

B. Proposals Pending

1. Source: National Science Foundation

Title: Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis

Amount: $365,047

Period: 10/15/84 - 4/15/88

Effort: 25% Academic
25% Summer

Location: Georgia Institute of Technology, School of Mechanical Engineering

The University of Chicago, Departments of Surgery and Pathology

2. Source: Veterans Administration

Title: Blood Velocity and Spectra Estimation from Doppler Ultrasound

Amount: $115,240

Period: 7/1/86 - 6/30/88

Effort: 20% Academic
20% Summer

Location: Georgia Institute of Technology, School of Mechanical Engineering

Veterans Administration Medical Center, Atlanta, Georgia

3. Source: National Institutes of Health

Title: Molecular Mechanisms of Hyperlipemia and Atherogenesis (This is a proposal from The University of Chicago. Georgia Tech is a subcontractor on a portion of this application.)

Amount: $1,120,409 (Amount of Georgia Tech subcontract for 5 year period)

Period: 12/1/86 - 11/30/91

Effort: 30% Academic
30% Summer

Location: Georgia Institute of Technology, School of Mechanical Engineering

The University of Chicago, Departments of Surgery and Pathology

C. Proposals Planned

1. None